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Published in:
Medical Hypotheses

DOI:
10.1016/j.mehy.2015.12.013

Publication date:
2016

Medical Hypotheses 87 (2016) 14–21

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Circuits regulating pleasure and happiness in major depression

A.J.M. Loonen [a,*], S.A. Ivanova [b]

[a] Department of Pharmacy, University of Groningen, The Netherlands
[b] Mental Health Research Institute, and National Research Tomsk Polytechnic University, Tomsk, Russian Federation

ARTICLE INFO

Article history:
Received 16 August 2015
Accepted 15 December 2015

ABSTRACT

The introduction of selective serotonin reuptake inhibitors has gradually changed the borders of the major depression disease class. Anhedonia was considered a cardinal symptom of endogenous depression, but the potential of selective serotonin reuptake inhibitors to treat anxiety disorders has increased the relevance of stress-induced morbidity. This shift has led to an important heterogeneity of current major depressive disorder. The complexity can be disentangled by postulating the existence of two different but mutually interacting neuronal circuits regulating the intensity of anhedonia (lack of pleasure) and dysphoria (lack of happiness). These circuits are functionally dominated by partly closed limbic (regulating misery-fleeing behaviour) and extrapyramidal (regulating reward-seeking behaviour) cortico-striato-thalamo-cortical (CSTC) circuits. The re-entry circuits include the shell and core parts of the accumbens nucleus, respectively. Pleasure can be considered to result from finding relief from the hypermotivation to exhibit rewarding behaviour, and happiness from finding relief from negative or conflicting circumstances. Hyperactivity of the extrapyramidal CSTC circuit results in craving, whereas hyperactivity of the limbic system results in dysphoria.

Introduction

In psychiatry, the term anhedonia (Greek: αν- *an*-, "without" + ήδονή *hēdonē*, "pleasure") describes the inability to experience pleasure from usually enjoyable activities, such as exercise, hobbies, sexual activities, or social interactions [1]. In the 1960s and 1970s, anhedonia was considered a core symptom of "endogenous" depression. It was also included as a main criterion for the diagnosis of major depressive disorder (MDD) with melancholia, according to the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III), published in 1980 [2,3]. MDD with melancholia was considered to be a specific subtype of depression known to respond preferentially to biological treatment, which in those days included tricyclic antidepressant drugs and electroconvulsive therapy [3].

Shortly after publication of the DSM-III, selective serotonin reuptake inhibitors (SSRIs) were marketed, changing the borders of the MDD disease class. SSRIs appear to be therapeutically active in certain anxiety disorders, such as panic disorder and obsessive–compulsive disorder [4]. This efficacy indicates that the serotonin system is very involved in stress and worrying; more accurately, drugs that interfere with the activity of the serotonergic system can be used to treat disorders that are accompanied by stress reactions and cognitive anxious and/or depressed symptoms. Symptoms of anxiety and depression commonly co-occur [5], and at least some evidence has been found for shared genetic aetiologies between these conditions [6]. Moreover, experiments with 'serotonergic' interventions led to the defining of a new subtype of depression, designated as 'anxiety/aggression-driven depression' [7].

The potential of SSRIs for treatment of both MDD and anxiety disorders resulted in a broadening of the depression concept and probably induced considerable heterogeneity within the class of disorders currently referred to as MDD. However, attempts to cluster this variety of symptoms in separate classes of depressive disorder have not been very fruitful [8]. Melancholic symptoms (including pervasive anhedonia) remain key features in distinguishing an "endogenous" subtype from other forms of depression [2,9]. Using specific symptoms to discriminate between additional and/or overlapping subtypes seems to be pointless.

In our opinion, the problem can better be approached from the other direction, starting with the biological basis of subsets of depressive symptoms. We suggest taking a possible dysfunction of specific brain structures as the starting point for defining different components of depression that may differentially respond to different (pharmacological and/or psychological) treatments.

* Corresponding author at: Department of Pharmacy, Antonius Deusinglaan 1, 9713AV Groningen, The Netherlands. Tel.: +31 50 363 7675; fax: +31 50 363 2772.
E-mail address: a.j.m.loonen@rug.nl (A.J.M. Loonen).

http://dx.doi.org/10.1016/j.mehy.2015.12.013
0306-9877/

In this paper, we postulate the existence of two different neuronal circuits regulating different aspects of depressive disorder and propose to distinguish two, mutually interacting components of depression. According to one component, depression can be considered to be a 'worrying' disorder, characterized by many cognitive symptoms, including feelings of hopelessness and negative expectations. According to the other component, depression can be considered to be a 'lust' disorder, characterized by loss of energy and motivation, as well as by anhedonia. The symptoms of these two components largely overlap and they can possibly best be considered as the two theoretical endpoints of a depressive disease continuum. In addition, they interact with each other in a yin-and-yang fashion. However, considering depression as consisting of two such components may offer interesting starting points for research into (e.g., neuroendocrine and neuroimmunological) biomarkers of depression and the interaction of brain structures during drug treatment and psychotherapy. To facilitate a clear description of the neuronal circuits involved, we will first briefly describe a specific model for the cerebral organization of the behavioural response systems.

The behavioural response systems

Basic starting points

In its most essential form, behaviour can be considered as an adaptive reaction of the organism to important stimuli from the environment. Within the brain, input from the senses (in humans, also cognitions) is transformed into a specific, partly behavioural, output as a reaction to the conditions within the individual's biosphere.

This capability to respond to environmental circumstances must be very ancient. Even the most primitive freely moving animals living in the oceans at the beginning of the Cambrian explosion over 540 mya must have been capable of feeding, fighting, hiding, and mating in order to survive as individuals and as a species. Therefore, their primitive brains must have been able to regulate these processes. We have recently described the evolution of the circuits controlling reward-seeking and misery-fleeing behaviours [10]. The earliest vertebrates had a forebrain with a quite modern extrapyramidal system that could induce the above behaviours by giving direct output to motor control centres within the brainstem. These animals still lacked neocortical regulatory control structures. The input of this extrapyramidal system was predominantly olfactory. The activity of the extrapyramidal system was regulated by monoaminergic fibres coming from the lower diencephalon and upper brainstem. These fibres reinforced appetitive-seeking behaviour or flight behaviour resulting from negative input. More recently, vertebrates developed limbs and invaded the continents, a lifestyle that required numerous new skills. This acquisition resulted in the further development of a large forebrain with its neo-cortical and neo-subcortical structures for adequately processing complex input and generating adequate (and also far more complex) output [10,11]. Nevertheless, the primary functions were probably retained within the brainstem, diencephalon and subcortical forebrain (mainly ventral striatum, amygdala, and hippocampus).

These considerations make it plausible that in modern humans, the aforementioned basic emotional functions are also primarily regulated by embryological 'early' developed parts of the nervous system within the forebrain, primarily the archipallium (hippocampus) and archistriatum (nuclear amygdala), with only parts of the paleopallium [12]. The limbic areas arising from these early structures are probably still primarily responsible for the emotional response type in the adult brain.

Emotional response regulation

A suitable model for the regulation of the emotional response can be derived from the paper of Terence and Mark Sewards [13]. According to their model, the control centre for emotional response types like *sexual desire*, *hunger*, *thirst*, *fear*, *nurturance*, *sleep-need drives* and *power-dominance drives* is the hypothalamus. The output of the hypothalamus proceeds along three channels. The first route projects via the thalamus to the cortex, including a pathway that contributes to the perception of emotion and one for the initiation and planning of cognitive and motor responses (drives). The second output pathway is a projection at least partly via the periaqueductal grey (PAG) to several brainstem nuclei, including nuclei that regulate the autonomic components of the emotional response (e.g., increased circulation and respiration). The PAG also activates the serotonergic raphe nuclei, the adrenergic locus coeruleus complex, and the dopaminergic ventral tegmental area [13–16]. From these nuclei, projections pass back to the hypothalamus (e.g., regulating hypophysiotropic hormones) and through the medial forebrain bundle to the forebrain (activating the frontal cortex). The PAG also constitutes an important input structure generating signals to the emotional forebrain [17]. Apart from hormone release mediated through various brainstem nuclei, a third direct hypothalamic projection system regulates the endocrine component of the emotional response, enabling adaptation of the milieu interne, or correction of a possible misbalance. The hypothalamus also exerts a receptor function for various substances in the circulating blood [18].

This model corresponds to a significant extent with the model of Mario Liotti and Jaak Panksepp [19]. However, they follow a different approach, describing seven emotional systems for *seeking*, *rage*, *fear*, *panic* (separation distress and social bonding), *care* (nursing and empathy), *lust* (sexual love), and *play* (joy and curiosity), which are not all regulated by the autonomic hypothalamus. Within the context of this article, the first three systems deserve a more detailed description.

The appetitive motivation *seeking* system stimulates the organism to acquire the many things needed for survival [19]. This motivation is coupled to a reward feeling that can—but not necessarily does—result from these activities. The nature of the specific rewards is of a lesser importance; the system works equally well for seeking food, water, warmth, and illicit drugs, as well as for social goals like sexual gratification, maternal engagement, and playful entertainment. The system promotes interest, curiosity, and desire for engagement with necessary daily life activities [19]. The process of reward pursuing consists of at least three psychological components: learning to value (attentive salience), incentive salience or 'wanting', and experiencing pleasure resulting in 'liking' [20,21]. The first component is believed to be addressed by the amygdala [22,23]. The amygdala can 'learn' to appreciate sensory appetitive information within the context of external and internal circumstances and to initiate a proper response. The second component is regulated by mesocorticolimbic mechanisms [20], with a central role for the nucleus accumbens (NAcb) [24,25]. Important neural substrates for this system are dopaminergic mesolimbic and mesocortical projections coming from the ventral tegmental area [26,27]. The latter also determines the physical link between the possibility of experiencing pleasure and the development of addiction [28].

The amygdala additionally takes a central position with respect to valuing aversive stimuli [22,23], playing a critical role in anxiety and aggression. The anger-promoting *rage* system is associated with irritation and frustration [19]. In this system, the emotional circuit is stimulated by projections between the medial amygdala and the medial hypothalamus via the stria terminalis [29]. Neurons also project reciprocally between specific parts of the PAG in the

mesencephalon and the medial hypothalamus. The *fear* system is organized in a fashion parallel to the rage system, in which both the amygdala and the PAG project to the medial hypothalamus [30,31]. Activity within this system can lead to freezing or flight behaviour. Sustained fear (anxiety) is also mediated by the amygdala, but follows a slightly different anatomical route [30] and links the fear and stress systems.

Taken together, the regulation of the described forms of emotional output can be summarized and simplified into the scheme in Fig. 1. The hypothalamus can be considered one of the principle control centres for emotional (non-behavioural) output (especially gratification, fear, and aggression-driven). As explained above, the hypothalamus itself receives a stimulating input function from the amygdala, among other regions. The amygdala is responsible for the initiation of a suitable response type. In this process of initiating the emotional response, the amygdala is inhibited by the medial prefrontal cortex [32–34]. This scheme describes the process of response selection, but another mechanism is regulating the level of motivation to exhibit the selected response type.

Limbic regulatory system

The abovementioned model (Fig. 1) concentrates the controller role of the complex emotional response within the hypothalamus and its initiator function within the amygdala [35]. The amygdala consists of a heterogeneous group of nuclei and cortical regions and is divided into cortical (basolateral) and ganglionic (centromedial) sections [22,36,37]. The various nuclei differ in the number and type of brain areas to which they are connected (Fig. 2). Apart from extensive connectivity with a variety of cortical areas [36], the various parts of the complex are mutually massively connected with each other [36,37]. Nevertheless, it is possible to consider the centromedial part as an output channel to the diencephalon and brain stem, while the basolateral part is more easily regarded as an input channel for cortical information (Fig. 2). Moreover, the amygdaloid complex has widespread connectivity with many subcortical regions [36], including the dorsal and ventral striatum, the bed nucleus of the stria terminalis, and the basal forebrain nuclei. The centromedial amygdala is continuous with the extended amygdala, which is in turn continuous through the bed nucleus of the stria terminalis with the shell part of the NAcb [38,39]. This extended amygdala takes a position to the allocortex (olfactory cortex and hippocampus) that is similar to that which the neocortex takes to the striatum [39]. This idea can be extended to distinguishing limbic and extrapyramidal basal ganglia. The centromedial amygdala, proper extended amygdala, bed nucleus of the stria terminalis, and the shell of the NAcb form the limbic basal ganglia, with a function for the limbic cortex that reflects that of the extrapyramidal basal ganglia for the rest of the neocortex (Fig. 3).

A neurobiological model of depression

Investigations using *in vivo* neuroimaging methods have demonstrated that the depressive syndrome is probably best conceptualized as a disorder rooted in a dysfunction of neuronal circuits [40]. This formulation means that a depressive episode should be considered to result from failed network regulation under circumstances of cognitive, emotional, or somatic stress [41]. Moreover, depression is not only caused by the failure of one discrete network but also involves the inability of the remaining system to maintain homeostasis. Mayberg and co-workers developed a limbic–cortical dysregulation model to explain neuroimaging findings in three behavioural states: baseline depressed, post-treatment (medication, cognitive therapy, placebo, surgery), and transiently induced sadness [41,42]. A key structure in their model is the infralimbic subgenual anterior cingulate cortex (Cg25). Activity in this area increases with sad mood and decreases following response to several antidepressant biological treatments.

An important limitation of their work is the use of SSRIs for their 'post-treatment with medication' condition. However, SSRIs may have dissimilar antidepressant effects in comparison to tricyclic antidepressants [43]. As described in the introduction, SSRIs more specifically have efficacy in many stress disorders [4]. Selective norepinephrine uptake inhibitors are devoid of this activity [44].

Based on the integration of five current theories that explain how dysfunction of neurobiological processes may result in the development of a depressive mood disorder, we have developed a different model [45]. Integrating the amine, biorhythm, neuroendocrine, neuroimmunological, and kindling hypotheses of depression, we hypothesize two interacting depression mechanisms

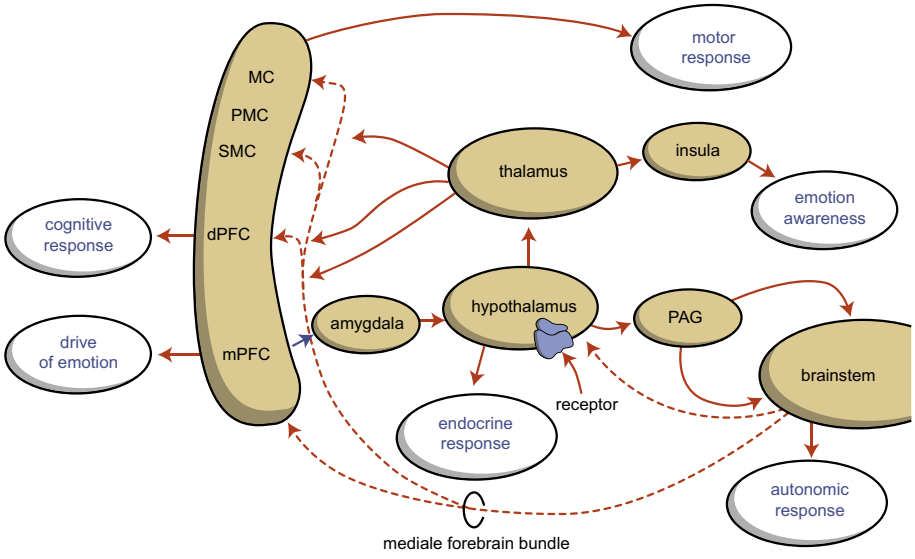

Fig. 1. Simplified model for the regulation of emotional response. The hypothalamus is considered to be the principle controller and the amygdala the initiator of emotional response. In this depiction, the amygdala represents all limbic structures involved in emotional response. PAG = periaqueductal grey substance.

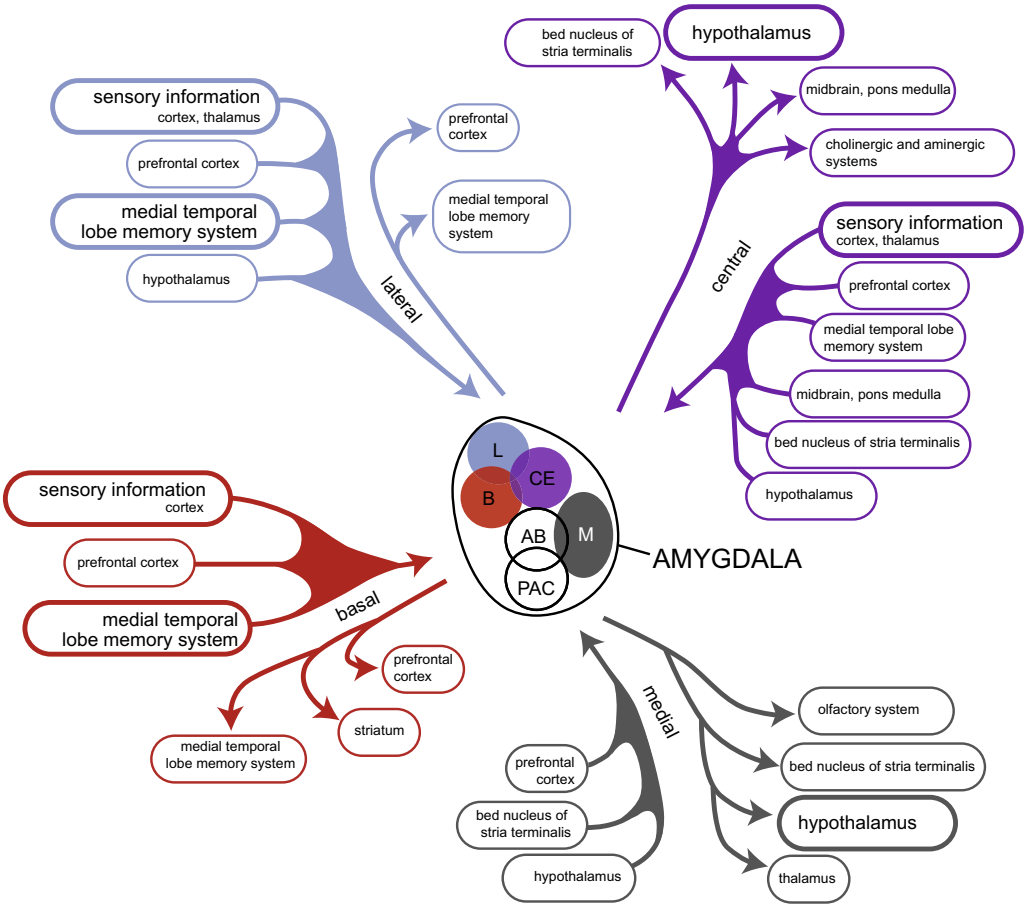

Fig. 2. Connections of the four sections of the amygdaloid nucleus. The various amygdaloid nuclei differ in the areas to which they are connected (adapted from Ref. [37], reproduced with permission of the author).

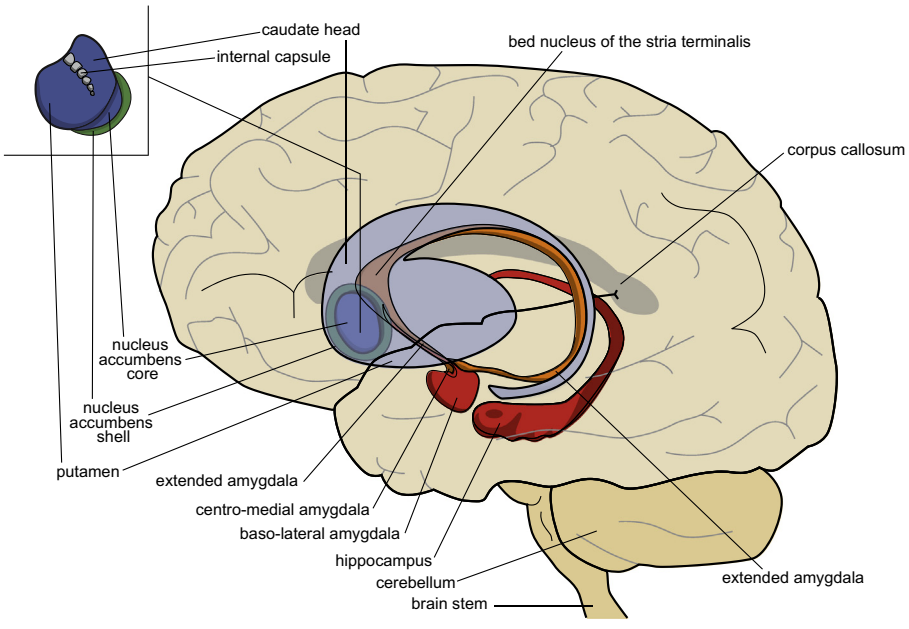

Fig. 3. Position of the limbic basal ganglia (centromedial amygdala, extended amygdala, bed nucleus of the stria terminalis, and nucleus accumbens shell) relative to the extrapyramidal basal ganglia and hippocampus.

that correspond to depression as a 'lust' disorder, characterized by lack of energy and pleasure, and as a 'worrying' or 'concern' disorder, characterized by feelings of uselessness and hopelessness. The first type of depression can be associated with dysfunction of brainstem, diencephalon, and extrapyramidal basal ganglia, and the second with dysfunction of limbic cortical areas (including

the basolateral amygdaloidal complex) and the hippocampal complex. According to our model, subcortical structures play a dominant role in generating pathological mood conditions.

Role of the extrapyramidal basal ganglia

The 'extrapyramidal system' is often mainly associated with motor activity but also regulates other behavioural responses. The first station of this circuit is formed by the striatum, which consists of three parts that correspond to three parallel divisions of the extrapyramidal system (Fig. 4): the caudate nucleus (cognitive system), putamen (motor system), and ventral striatum (emotional/motivational system) [38,46–48]. This last part is formed by the NAcb, which consists of a core ($NAcb_C$) and a shell ($NAcb_S$). The core belongs to the extrapyramidal basal ganglia, and is primarily involved in motivating the organism to exhibit skilled behaviour. The shell belongs to the limbic basal ganglia and is primarily involved in facilitating intuitive behaviour [38,48].

Only the most posterior part of the circuits is shown in Fig. 4. In reality, in each circuit, information from different cortical areas converges within the circuit to influence a specific point of the frontal cortex [46,47]. This architecture also results in five segregated cortical-subcortical re-entry circuits, one each for motor, oculomotor, and executive lateral prefrontal function, and two circuits (anterior cingulate and orbitofrontal) for emotional-motivational functions [46,47]. The motivational re-entry circuit runs through the $NAcb_C$, which is activated by the anterior part of the anterior cingulate cortex (aCg, BA24) and the orbitofrontal cortex (e.g., BA11) [48–50]. Although not yet proven, an emotional re-entry circuit could be postulated to exist with its first station in the $NAcb_S$, which is activated by the infralimbic subgenual cingulate (BA25) and the orbitofrontal cortex (Fig. 5). These last two structures are essential for our depressive state model. Activation of the $NAcb_C$ circuit results in behaviour that may finally result in reward. This activation is accompanied with feelings, as exhibited in a very pure (although pathological) form of 'craving' illicit drugs [28]. Relief from this feeling may be postulated to be experienced as 'pleasure' or 'lust.' Dysfunction of this circuit can be expected to result in demotivation to exhibit rewarding behaviour

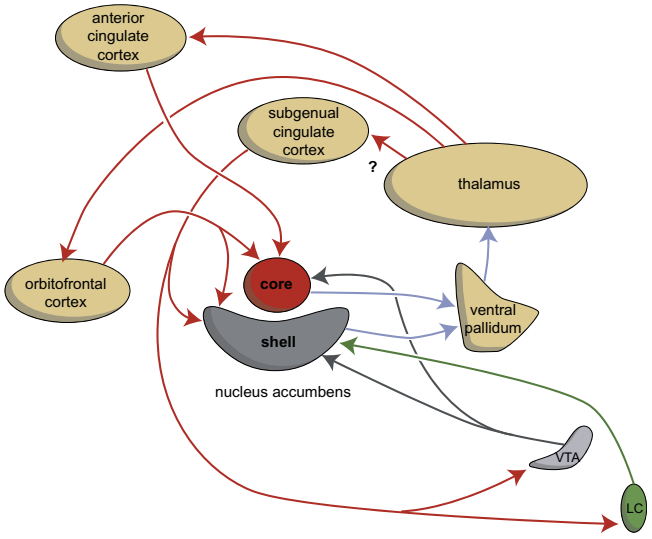

Fig. 5. Stimulation of the core and shell of the nucleus accumbens. (Adapted from Ref. [49], reproduced with permission of the author). VTA = ventral tegmental area (dopaminergic); LC = locus coeruleus (adrenergic).

(lack of energy) and the inability to experience pleasure (anhedonia). Activation of the $NAcb_S$ circuit leads to an unpleasant urge to solve a significant problem [50]; the emotion that corresponds to this behaviour is 'unhappiness' or 'dysphoria'. According to this hypothesis, depression as a 'lust' disorder is expected to be related to hypo-activity of the $NAcb_C$ system, while depression as a 'worrying' disorder is related to hyperactivity of the $NAcb_S$ circuit.

Two complementary circuit systems

We suggested distinguishing two types of basal ganglia: the extrapyramidal basal ganglia (caudate nucleus, putamen, $NAcb_C$; blue in Fig. 6) and the limbic basal ganglia ($NAcb_S$, bed nucleus of stria terminalis, extended amygdala, central medial amygdala; orange in Fig. 6). These belong to the complementary

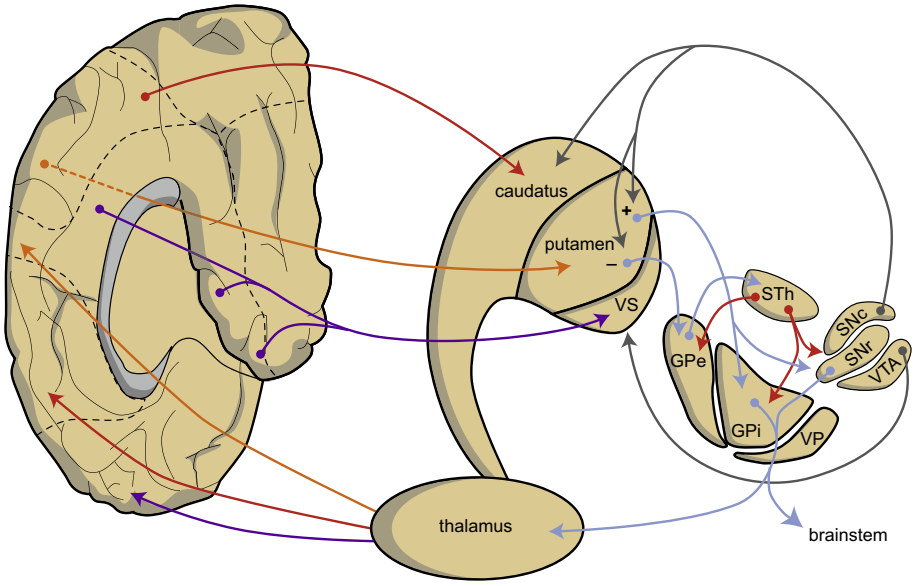

Fig. 4. Simplified representation of the posterior parts of three cortico-striato-thalamo-cortical circuits. Only connections of the putamen are shown. Red, orange, purple = glutamatergic; blue = GABAergic; grey = dopaminergic; VS = ventral striatum (largely accumbens nucleus); GPe = globus pallidus, external segment; GPi = globus pallidus, internal segment; VP = ventral pallidum; STh = subthalamic nucleus; SNc = substantia nigra, pars compacta; SNr = substantia nigra, pars reticulata; VTA = ventral tegmental area.

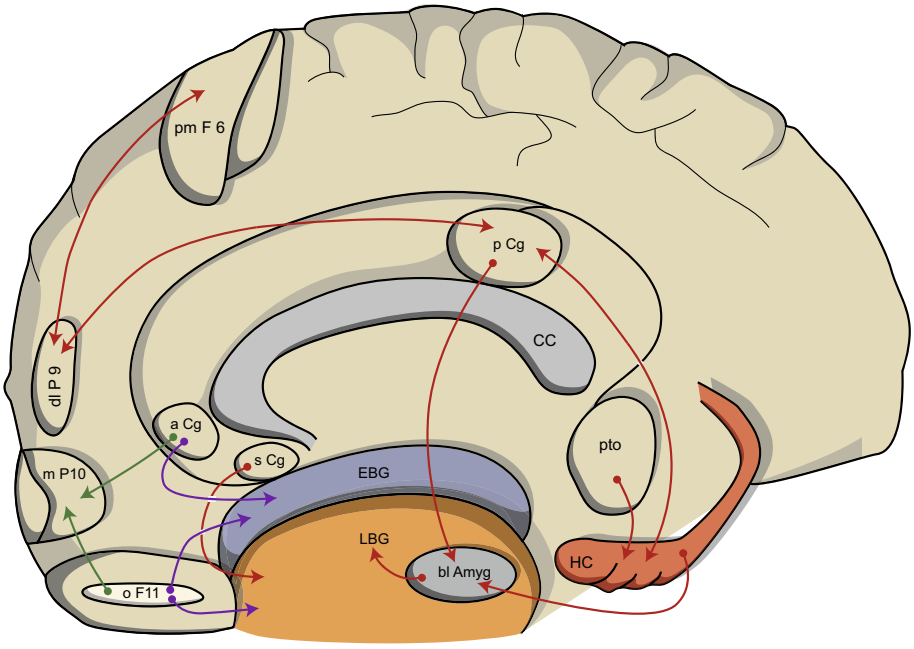

Fig. 6. Model of the regulation of the extrapyramidal and limbic cortico-subcortical behaviour-regulating circuits. aCg = anterior cingulate cortex (Brodmann's area (BA) 24); blAmyg = basolateral amygdaloid complex; CC = corpus callosum; dlP9 = dorsolateral prefrontal cortex (BA9/46); EBG = extrapyramidal basal ganglia (caudate nucleus, putamen, accumbens nucleus core); HC = hippocampus complex; LBG = limbic basal ganglia (accumbens nucleus shell, bed nucleus of the stria terminalis, extended amygdala, centromedial amygdala); mP10 = dorsomedial prefrontal cortex (BA9/10); oF11 = orbitofrontal cortex (BA11); pCg = posterior cingulate cortex (BA23/31); pmF6 = posterior dorsolateral prefrontal cortex (BA6); pto = parietal temporal occipital association cortex (BA22/39/40); sCG = subgenual cingulate cortex (BA25).

extrapyramidal and limbic circuit systems. The extrapyramidal system originates from the entire neocortex, including a few limbic areas. This circuit runs from the cerebral cortex to the striatum and finally through the dorsal thalamus to frontal (anterior) areas of the cerebral cortex [46]. It consists of topographically arranged, more or less segregated, converging circuits and contains the five re-entry circuits described above [38]. We postulate the existence of a second, limbic circuit system. This limbic circuit starts in allocortical areas of the cerebral cortex, hippocampus complex [39], and basolateral part of the amygdala and runs through the limbic basal ganglia to the hypothalamus and (directly or thereafter) thalamus. From there, some projections run to the mesial part of the frontal cerebral cortex [13,51] and the insula [52].

As an interface between these systems, two circuits involving the $NAcb_C$ and $NAcb_S$ are positioned (Fig. 5). It remains to be demonstrated whether or not some of the fibres running through the $NAcb_S$ are members of a sequential cortical-subcortical-cortical re-entry circuit. The subgenual cingulate cortex (BA25) receives thalamic afferents from the mediodorsal, paratenial, and reuniens nuclei [53]. We postulate the existence of a circular causal relationship between the dysfunctioning of limbic cortical circuits as described by Mayberg and colleagues [41,42] and the two cortical-basal ganglia-thalamic-frontal cortical circuits described above.

The two circuits running through $NAcb_C$ and $NAcb_S$ are complementarily active and interact with each other in a yin-and-yang fashion. The first motivates reward-seeking and the second misery-fleeing behaviour.

Implications: two interacting substrates for depression

Accepting this model of MDD, consisting of two components that are regulated by different cortical-subcortical-cortical circuits, offers interesting starting points for brain imaging research. There are many benefits of this hypothesis when we try to explain the pathophysiology of clinical events of mood disorders. For example, individual differences in the efficacy of antidepressants might depend on the varying degrees of damage of these neuronal circuits of each patient. It would be interesting to study the acute and chronic effects of more or less selective serotonergic (citalopram), noradrenergic (reboxetine), and dopaminergic (modafinil) antidepressants and certain specific receptor agonists or antagonists with neuroimaging techniques, specifically addressing these anatomical structures in patients with the broadly defined depressive disorder according to DSM-5. The $NAcb_S$ receives adrenergic input from fibres coming from the locus coeruleus which stimulate β-adrenoceptors (Fig. 5) [50,54]. Down-regulation of postsynaptic β-adrenoceptors is a consistent and robust effect of chronic treatment with most antidepressants, and this effect is accelerated by co-treatment with SSRIs [55]. Thus, chronic treatment with antidepressants may result in decreasing the activity of the limbic re-entry circuit and promoting the activity of the circuit, which includes the $NAcb_C$. In 1987, Den Boer et al. described that depressive symptomatology reacted more efficaciously to clomipramine, which has an adrenergic component, than to the SSRI fluvoxamine when patients were treated for anxiety disorders [56]. The antidepressant effects of SSRIs may be related to down-regulation of 5-HT2C receptors within other parts of the limbic circuit (most likely the cortical amygdala and/or hippocampus). At the onset of treatment, indirect activation of 5-HT2C receptors participates in the anxiogenic effects of selective 5-HT reuptake inhibitors (SSRIs) as well as their inhibition of sleep, sexual behaviour and appetite [57]. This condition is also known as the "jitteriness/anxiety syndrome" [58]. Conversely, progressive down-regulation of 5-HT2C receptors parallels the gradual onset of clinical efficacy of SSRIs [57]. This down-regulation may result in decreased sensitivity to fear- or stress-inducing input and decreased activity of the limbic circuit, which may explain both the antidepressant and anxiolytic activity of SSRIs.

It would be scientifically interesting and clinically relevant to find out whether certain pharmacological interventions result in preferential amelioration of symptoms related to dysfunction of one of the two subcortical circuits in comparison to others, and whether such effects are predicted by different biomarkers. Immunological biomarkers may be more closely linked to hyperfunction of the limbic subcortical circuit because this system is involved in motivation to escape from misery. Can specific subtypes of depression (e.g., bipolar depression) be identified that respond better to noradrenergic or dopaminergic drugs? Specific receptor ligands to modulate the activity of the extrapyramidal and limbic circuits are readily available, and this strategy may give far quicker results than classical clinical trials. The mixed state of bipolar patients might depend on the co-hyperactivity or co-hypo-activity of these circuits.

Regulation of activity

We have recently reviewed the literature covering how these circuits developed during evolution [10]. It should be realized that the first vertebrates, comparable to modern lampreys, had an extrapyramidal system that is quite comparable to that of humans [10,11]. However, the striatum of these creatures is best considered as the forerunner of the nuclear amygdala instead of the human striatum. Moreover, the lamprey habenula–projecting globus pallidum, a structure not clearly identified in humans, regulates the activity of dopaminergic projections from the midbrain to the striatum by influencing a pathway via the habenula and fasciculus retroflexus to the brainstem. We want to suggest that a similar system has been maintained in humans regulating the activity of the circuits motivating reward acquisition or escape from misery [10].

Conclusion: two interacting substrates for depression

According to our hypothesis (Fig. 6), two types of mechanisms can induce symptoms of depression. Activation of the extrapyramidal basal ganglia-containing circuit results in activation of the appetitive motivation seeking-system, which then results in craving for food, water, warmth, sex, illicit drugs, or social gratification. This process is accelerated by hyperactivity of a re-entry circuit starting in the orbitofrontal cortex. Hypoactivity of this structure prevents the individual from experiencing sudden relief from these feelings, which is sensed as pleasure or lust. Hypoactivity, therefore, results in a lack of motivation and anhedonia as symptoms of depression. Activation of the limbic basal ganglia-containing circuit results in an urge to find relief from distress induced by internal or environmental circumstances. These unpleasant feelings are described as dysphoria or unhappiness. It is hypothesised that this process is accelerated by hyperactivity within a re-entry circuit starting in the subgenual anterior cingulate. These two circuits do not function independently, and their activities are adjusted to the current circumstances by a regulatory system involving the habenula.

Conflict of interest

The development of this commentary was supported in part by the Russian Foundation for Basic Research, project 14-04-01157a, "The search for biomarkers of depressive and mood disorders." A. J.M.L. received a speaker's fee and an unconditional research grant from Servier Pharma Netherlands. SAI has nothing to disclose.

Acknowledgements

The manuscript was edited and proofread by San Francisco Edit (www.sfedit.net).

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